

## EDITORIAL COMMENT

### Asymptomatic Wolff-Parkinson-White Syndrome: Is it Time to Revisit Guidelines?\*

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Current guidelines (1) and expert opinion (2) do not recommend routine electrophysiologic (EP) study in patients with asymptomatic Wolff-Parkinson-White (WPW) syndrome. Patients who engage in "high-risk" occupations or those patients in whom a pre-excitation pattern precludes them from following their chosen career may be exceptions. In this issue of the *Journal*, Pappone et al. (3) report the results of a five-year follow-up of a cohort of 212 patients with asymptomatic WPW. During the follow-up period, one patient died from ventricular fibrillation (VF), and two patients had a cardiac arrest due to VF from which they were successfully resuscitated. These findings contrast to previous studies (4–14) that have found asymptomatic WPW to be associated with a good prognosis (Table 1). In light of the findings of Pappone et al. (3), it is important to ask whether we should re-address the issue of routine EP testing for asymptomatic WPW.

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The study of Pappone et al. (3) is commendable for recruiting patients that were genuinely asymptomatic at the time of diagnosis. Evidence of the WPW pattern was found incidentally in all patients either at a routine medical examination or on a screening electrocardiogram before admission to competitive sport or a high-risk occupation. All patients underwent a baseline EP study and a repeat EP study after five years of follow-up or earlier if symptoms developed. Unfortunately, a large number of patients (50 patients) are excluded from the final analysis.

Over the period of the study, a number of patients became symptomatic (33 of 162 patients, 20.4%). These patients were, on average, younger than those who did not become symptomatic ( $20.1 \pm 8.6$  years vs.  $37.1 \pm 13.4$  years,  $p < 0.0001$ ). At the initial EP study, 29 of these 33 (88%) patients had inducible atrioventricular re-entrant

tachycardia (AVRT). Atrioventricular re-entrant tachycardia degenerated into pre-excited atrial fibrillation (AF) in 11 of these 29 patients, with a mean shortest pre-excited RR (SPRR) interval of 223 ms. After the onset of symptoms, spontaneous arrhythmias were documented in all 33 patients, in the form of supraventricular tachycardia in 25 patients and AF in 8 patients. All eight patients with spontaneous AF had both inducible AVRT and pre-excited AF during the initial EP study. It is interesting to note that only 1 of the 30 patients with inducible AVRT at the initial study remained asymptomatic, and only 4 of the 115 noninducible patients developed symptoms during follow-up. The occurrence of nonsustained AF (17 patients) after rapid atrial pacing at the initial EP study was not a good predictor of future symptoms. Importantly, the three patients who had a VF arrest had both AVRT and AF at the time of the initial EP study and documented spontaneous AF during follow-up. All had been offered ablation after the recognition of spontaneous AF but had declined.

In addition to assessing the inducibility of tachycardia, the initial EP study highlighted other factors that suggest a patient may subsequently develop symptoms. The presence of multiple accessory pathways (APs) (15/33 vs. 1/129,  $p < 0.0001$ ) suggests that the patient is more likely to become symptomatic. Multiple APs are also known to increase the risk of VF in WPW patients (15) and were present in all three patients who subsequently had VF. A shorter antegrade effective refractory period of the AP was also associated with symptoms during follow-up, although this was a much weaker predictor than multiple pathways or inducible AVRT.

The authors conclude that, in asymptomatic WPW, a negative EP study identifies subjects at low risk of future arrhythmic events (AVRT, AF, and VF), and that EP testing is a valuable tool in predicting future arrhythmias. A positive EP study (inducible sustained or nonsustained AVRT and/or AF) has positive and negative predictive values of 87.9% and 86.0% for the prediction of future arrhythmic events. It is noteworthy that AF was induced in only 17% of patients studied, which is considerably less than in previous series (7).

Do these findings provide a compelling argument for routine EP testing of all asymptomatic WPW patients? The principal argument for EP testing of asymptomatic WPW patients is to identify patients at risk of subsequent VF, rather than to identify those that may become symptomatic later in life, as occurrence of any other arrhythmia by and large provides abundant opportunity to direct curative treatment at those who have declared themselves. Although all the patients were asymptomatic at the time of diagnosis, the three patients who subsequently had VF in this study all developed symptomatic AF before this event. If one had pursued a strategy of selecting patients for EP testing at the development of symptoms, it is likely that no patient would

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**Table 1.** The Natural History of Asymptomatic WPW

Authors	Number of Patients	EP Study	Induced Arrhythmias		SCD	Follow-up (yrs)
			AVRT	AF SPRR		
Electrophysiology-Based Studies						
Klein (4)	29	yes	17%	31%	0	4.5*
Satoh (5)	34	yes	18%	3%	0	1.3
Beckman (6)	15	yes	20%	13%	0	7.5
Leitch (7)	75	yes	16%	31%	0	4.3*
Fukatani (8)	64	yes	n/a	n/a	0	6.6
Brembilla-Perrot (9)	40	yes	7.5%	12.5%	0	1.8
Population-Based Studies						
Berkman (10)	128	no	13.3% → symptoms		0	18
Soria (11)	78	no	n/a		2	5.7
Munger (12)	53	no	21% → symptoms		0	10.1
Goudevenos (13)	77	no	4% → symptoms		0	4.6
Fitzsimmons (14)	187	no	15% → symptoms		0	21.8

\*There is some overlap in the patients reported in these two studies.

AF SPRR = atrial fibrillation with a shortest pre-excited RR interval of <250 ms; AVRT = atrioventricular re-entrant tachycardia; EP = electrophysiologic; n/a = not quoted in paper; SCD = sudden cardiac death; WPW = Wolff-Parkinson-White syndrome.

have had VF, only 33 patients would have been ablated, and 129 patients would have been spared an invasive study.

Sudden cardiac death can be the first presenting symptom of WPW in some patients, which has been the basis of the argument for EP testing of asymptomatic patients. In the three largest series of WPW patients with VF published, VF was the initial presenting symptom in 3/25 patients (16), 6/23 patients (17), and 8/15 patients (18). It is, however, a rare initial presentation in patients over 30 years of age (16,19). The true incidence of VF in asymptomatic WPW is, of course, much lower than suggested by these studies, which all suffer from selection bias, as they were based in major cardiac centers. They, nonetheless, highlight the potential for VF to be the presenting arrhythmia in WPW.

Assessment of the future VF risk in an asymptomatic patient with WPW is not easy. Noninvasive markers of lower risk such as intermittent loss of pre-excitation (20), sudden loss of AP conduction on exercise stress testing (21,22), and loss of AP conduction after treatment with antiarrhythmic drugs (23) are limited by inadequate sensitivity or specificity and the low incidence of future adverse events. Invasive EP assessment also has drawbacks, as no single factor has both a high sensitivity and specificity for identifying at-risk individuals. For instance, an SPRR of <250 ms during sustained induced AF is a very sensitive (16), but not specific, marker of the risk of VF in WPW patients, as approximately one-third of patients (7,9) with asymptomatic WPW will have an SPRR of <250 ms during induced AF. The presence of inducible AVRT, although less directly linked to the mechanism of VF than the short pre-excited RR intervals in AF, is a more specific marker of future symptoms and VF risk. The generally accepted mechanism for sudden cardiac death in WPW is the onset of AVRT that degenerates into AF then into VF (16,17). The likelihood of an asymptomatic WPW patient

having sustained AVRT in the future is much greater if the AP can conduct retrogradely (7) or sustain AVRT (6) at EP study. In the current study (3), inducible AVRT that degenerated into AF occurred in all three patients who subsequently had VF.

Short pre-excited RR intervals in AF (<250 ms) have traditionally received more attention as a risk factor for VF than inducible AVRT. This is reasonable because it is almost a universal finding in patients with VF. Studies of WPW patients with VF have focused primarily on comparing VF patients to symptomatic WPW patients without VF. Inducible AVRT was present at EP study in most patients in both groups and, therefore, was not identified as a strong independent marker of future risk. However, the situation is different in asymptomatic WPW where the presence of inducible AVRT, especially when it triggers AF, represents a more specific marker for future symptoms and VF risk.

The basic premise of investigating and treating an asymptomatic patient is, first, to do no harm. In the current era of radiofrequency (RF) ablation, a combined diagnostic and therapeutic procedure has become standard clinical practice. If routine EP testing of all asymptomatic WPW patients is considered, we must recognize that many patients will proceed immediately to RF ablation. Approximately one-third of patients will have an SPRR of <250 ms during induced AF, and, in others, there will be a strong temptation to ablate when catheters are in place. This greatly increases the risk to the patient. Most complications of a diagnostic EP study are minor and non-life-threatening. However, RF ablation is associated with serious complications such as myocardial infarction, stroke, cardiac tamponade, requirement for urgent cardiac surgery, and death. The rates of significant complications during RF ablation of APs reported in the Multicentre European Radiofrequency Survey (MERFS) (24), the 1993 North American Society of

**Table 2.** Complications of Radiofrequency Ablation

Studies	No. of Patients	Comp Rate	Perforation/ Tamponade	Complete AV Block	MI	CVA	Death
MERFS (24)	2,222	98 4.4%	16 0.72%	14 0.63%	0 0	11 0.49%	3 0.13%
NASPE (25)	5,427	99 1.8%	7 0.13%	9 0.17%	3 0.06%	8 0.15%	4 0.07%
Atakr (26)	500	n/a	n/a	5 1%	n/a	1 0.2%	1 0.2%

AV = atrioventricular; CVA = cerebrovascular accident; Comp = complication; MERFS = Multicentre European Radiofrequency Survey; MI = myocardial infarction; n/a = not available; NASPE = North American Society of Pacing and Electrophysiology.

Pacing and Electrophysiology (NASPE) survey of catheter ablation (25), and from the Atakr study (26) are summarized in Table 2. An overall risk of around 2% is especially significant to an asymptomatic, young patient. We should also keep in mind that the published results are likely to represent the better end of the spectrum, as they are based on voluntary registries from experienced high-volume centers.

Should the current guidelines be changed? It is difficult to make a strong recommendation for a strategy that, in the final analysis, will arguably result in comparable morbidity and mortality to the problem addressed. The key is a clear understanding by the patient of the relative merits of each strategy. The well-informed patient needs to choose between a very small risk over a long period of time and a one-time risk over a short span (i.e., ablation). Certain patients such as athletes and those in “higher-risk” occupations will generally choose ablation. Others, especially older patients (>30 years), may prefer the small risk of a conservative strategy. In the continuing absence of symptoms, the risk of future VF is low. The physician should also remember that the risks and success rates of ablation vary according to pathway location. Ablation of pathways in the septal area carries a significant risk of heart block, and ablation of left-sided pathways is associated with the risks of trans-septal puncture or the retrograde aortic approach. If an EP study is performed for risk stratification, the combination of inducible AVRT and a shortest pre-excited RR interval in AF of <250 ms provide the most compelling indications for ablation.

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